Overexpression **of** her - 2 / neu **in human** prostate cancer **and benign hyperplasia.**

Gu K; Mes-Masson A M; Gauthier J; Saad F
Centre de Recherche Louis-Charles Simard/Institut de cancer de Montreal, Quebec, Canada.

Cancer letters (IRELAND) Feb 6 **1996** , 99 (2) p185-9, ISSN 0304-3835--Print Journal Code: 7600053
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Overexpression of the **neu** oncoprotein has been described in several tumor models including breast and **prostate cancer** . **Overexpression** of **neu** has been reported to have prognostic significance in certain tumors but controversy continues regarding the role and frequency of **neu overexpression** in prostatic cancer. The objectives of the study were twofold. First, to characterize **neu** expression in **prostate cancer** in comparison to benign prostatic hyperplasia. Second, to determine whether **neu** expression correlates with Gleason grade in **prostate cancer** . Thirty-nine **prostate** cancers obtained from radical prostatectomy specimens and 10 benign prostatic hyperplasia specimens were included in the study. Specimens were formalin fixed and paraffin-embodied. **neu** expression was studied by immunohistochemical staining using a monoclonal **neu** specific AB-3 antibody. All 39 specimens (100%) of **prostate cancer** showed positive immunostaining of variable degree while 2 (20%) benign prostatic hyperplasia specimens showed positive staining. Thus, **neu** oncogene is **overexpressed** in localized **prostate cancer** compared to benign prostatic hyperplasia. The degree of **neu** immunostaining did not correlate with Gleason grade and there appeared to be a tendency towards an inverse relationship. The prognostic significance of the varying **overexpression** is unknown.

Overexpression **of** her - 2 / neu **in human** prostate cancer **and benign hyperplasia.**

... **1996** ,

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C-ERBB-2 ONCOPROTEIN OVEREXPRESSION **IN UTERINE CERVIX CARCINOMA WITH GLANDULAR DIFFERENTIATION - A FREQUENT EVENT BUT NOT AN INDEPENDENT PROGNOSTIC MARKER BECAUSE IT OCCURS LATE IN THE DISEASE** (Abstract Available)

Author(s): COSTA MJ; WALLS J; TRELFORD JD
Corporate Source: UNIV CALIF DAVIS,MED CTR,DEPT PATHOL,BLDG PAT 1,2315 STOCKTON BLVD/SACRAMENTO//CA/95817; UNIV CALIF DAVIS,MED CTR,DEPT OBSTET & GYNECOL/SACRAMENTO//CA/95817

Journal: AMERICAN JOURNAL OF CLINICAL PATHOLOGY, **1995** , V104, N6 (DEC), P 634-642
ISSN: 0002-9173
Language: ENGLISH Document Type: ARTICLE

Abstract: The c-erbB-2 proto-oncogene (**HER - 2 / neu**) codes for a transmembrane, tyrosine kinase, 185 kD oncoprotein (p185(erbB2)), which is related to the epidermal growth factor receptor, p185(erbB2) **overexpression** occurs in carcinomas at many sites, including the uterine cervix, and predicts poor clinical outcome. The authors hypothesize that p185(erbB2) immunohistochemistry will provide additional information in the evaluation of uterine cervix carcinomas with glandular differentiation (CCGD), a difficult and more frequent clinical problem. Paraffin sections from 82 CCGDs including 41 pure adenocarcinomas and 41 adenosquamous carcinomas (7 glassy cell predominant and 34 exhibiting a gland forming component) are immunostained with anti-p185(erbB2) (CB11 monoclonal, Novacastra Laboratories, Newcastle upon Tyne, UK). Seventy-seven percent of CCGDs exhibit p185(erbB2) immunoreactivity with distinct plasma membrane localization (M) in 50%, the remaining 27% show cytoplasmic staining only, Adjacent benign tissue is negative. The p185(erbB2) Staining intensity and distribution is as follows: 54.9% strong diffuse (SD, greater than or equal to 50% cells positive) with 40.2% M, 17.1% strong focal (SF, <50% cells positive) with 9.8% M, and 4.9% weak with no M. Immunoreactivity occurs in both squamous and glandular areas of adenosquamous carcinomas. Endometrioid histology is associated with absence of p185(erbB2) (P <.01); all other histopathologic features show no association, Follow-up information is available in 77 patients:

37 exhibit recurrent disease (8 pelvic, 15 distant and 14 both) at 1 to 144 months (mean 34, median 16) and 40 were disease free at 12 to 216 months (mean 75, median 64). Strong p185(erbB2) immunoreactivity predicts recurrence at 23 months (P <.05) but not overall recurrence at longer follow-up periods. Recurrent disease is associated with nuclear grade (P <.00001); high clinical stage (P <.001); vascular space invasion (P <.001); large size on clinical exam or pathologic evaluation (P <.005); and pelvic lymph node involvement (P <.05). Considering only patients in good prognosis groups, p185(erbB2) immunoreactivity does not predict recurrence. Strong p185(erbB2) immunoreactivity is associated with stage 3,4 disease (P <.01). p185(erbB2) expression is associated with CCGD carcinogenesis but occurs late in the disease, in patients who present at late stage, hindering its prognostic predictive value. p185(erbB2) immunolocalization may have a diagnostic role in confirming CCGD in histologically challenging cases, predicting high stage at initial biopsy, and defining therapeutic strategies.

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, 1995

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11/3,K,AB/5 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04514626 Genuine Article#: TJ447 Number of References: 48
Title: PAPILLOMAVIRUS, P53 ALTERATION, AND PRIMARY-CARCINOMA OF THE VULVA (Abstract Available)
Author(s): PILOTTI S; DAMATO L; DELLATORRE G; DONGHI R; LONGONI A; GIAROLA M; SAMPIETRO G; DEPALO G; PIEROTTI MA; RILKE F
Corporate Source: IST NAZL TUMORI,DIV ANAT PATHOL & CYTOL,VIA G VENEZIAN 1/I-20133 MILAN//ITALY/; IST NAZL TUMORI,DIV EXPTL ONCOL A/I-20133 MILAN//ITALY/; IST NAZL TUMORI,DIV DIAGNOST ONCOL/I-20133 MILAN//ITALY/ ; IST NAZL TUMORI,OUTPATIENT CLIN/I-20133 MILAN//ITALY/
Journal: DIAGNOSTIC MOLECULAR PATHOLOGY, **1995** , V4, N4 (DEC), P239-248
ISSN: 1052-9551
Language: ENGLISH Document Type: ARTICLE
Abstract: Twenty-nine samples from 28 cases of vulvar squamous cell carcinoma, of which 13 fulfilled the criteria of the bowenoid subtype (mean age 45 years, range 31-68) and 16 of the usual subtype of invasive squamous cell carcinoma (ISCC) (mean age 67.5 years, range 34-83) were investigated for human papillomavirus (HPV) DNA, TP53 alterations, and mdm2 and bcl-2 gene product deregulation, Microscopically all the bowenoid subtype cases (group I) showed a high-grade intraepithelial (VIN 3, carcinoma in situ) lesion associated with early invasive carcinoma in six cases and overt invasive carcinoma in one, By contrast, no evidence of early carcinoma was present in the ISCCs (group II). By in situ hybridization and/or Southern blot hybridization or polymerase chain reaction (PCR), HPV-DNA was detected in all cases of group I and in four of 16 cases (25%) of group II, two only by Southern blot after PCR. By single-strand conformation polymorphism and immunocytochemistry only wild-type TP53 and absence of detectable p53 product, respectively, were found in all cases of group I, i.e., in high-risk HPV-positive carcinomas, whereas mutations and/or p53 **overexpression** accounted for 75% in group II, i.e., in mainly HPV-negative carcinomas. The TP53 gene mutations observed in invasive carcinomas were significantly related to node-positive cases ($p = 0.04$). Taken together and in agreement with in vitro data, these results support the view that an alteration of TP53, gained either by interaction with viral oncoproteins or by somatic mutations, is a crucial event in the pathogenesis of vulvar carcinomas, but that TP53 mutations are mainly associated with disease progression. Finally, a preliminary immuno-cytochemical analysis seems to speak against the possible involvement of both MDM2 and BCL-2 gene products in the development of vulvar carcinoma.

, **1995**
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...Identifiers--POLYMERASE CHAIN-REACTION; SQUAMOUS-CELL CARCINOMA; TUMOR-SUPPRESSOR GENE; **CERVICAL - CARCINOMA** ; INSITU HYBRIDIZATION; INTRAEPITHELIAL NEOPLASIA; TRANSACTIVATION FUNCTION; MDM2 AMPLIFICATION; UTERINE CERVIX; E6 ONCOPROTEIN

Research Fronts: 93-7675 002 (WILD-TYPE P53; MDM2 GENE; C- **ERB** - **2** PROTEIN)
93-1530 001 (WILD-TYPE P53 PROTEIN; TUMOR-SUPPRESSOR GENES; E2F TRANSCRIPTION FACTOR)
93...
?

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S1      446515   (PROSTATE(2N)CANCER) OR ((RENAL OR KIDNEY)(2N)CARCINOMA) OR
              (CERVICAL(2N)CARCINOMA) OR LYMPHOMA
S2       22199   ERB2 OR (HER(W)2) OR NEU OR (ERB(W)2)
S3        1255   S1 AND S2
S4      225039   OVEREXPRESS?
S5         309   S3 AND S4
S6          97   S5 AND PY<=1997
S7          81   RD  (unique items)
S8      211428   PROSTATE
S9          56   S7 NOT S8
? s breast or mammary
          562352  BREAST
          139698  MAMMARY
     S10  660509  BREAST OR MAMMARY
? s s9 not s10
              56  S9
          660509  S10
     S11      12  S9 NOT S10
? t s11/3,k,ab/1-5
```

11/3,K,AB/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

09447924 PMID: 1281010

HER - 2 / neu **oncogene expression and DNA ploidy in normal human kidney and** renal **cell** carcinoma .

Danova M; Giordano M; Torelli F; Franchini G; Cappellano F; Riccardi A; Catanzaro F; Mazzini G

Dipartimento di Medicina Interna, C.N.R., Universita e IRCCS San Matteo, Pavia, Italy.

European journal of histochemistry - EJH (ITALY) **1992** , 36 (3) p279-88, ISSN 1121-760X--Print Journal Code: 9207930

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Using flow cytometry (FCM), we have investigated both the DNA content (stained with propidium iodide) and **HER - 2 / neu** oncogene expression (revealed by means of an anti- **HER - 2 / neu** monoclonal antibody) in neoplastic and non-neoplastic kidney samples from 20 patients with **renal** cell **carcinoma** . All the non-neoplastic samples and 15/20 (75%) renal cell cancers showed diploid modal DNA content while the remaining 5 neoplastic sample (25%) showed both diploid and hyperdiploid cell populations. In normal kidney the level of **HER - 2 / neu** oncoprotein was low (median fluorescence values in arbitrary units = 7.5 AU, range: 4-10 AU). In diploid renal cancers the level of **HER - 2 / neu** was slightly increased (median fluorescence values = 20 AU, range: 9.5-30 AU) ($p < .005$). The relationship of **HER - 2 / neu** expression to the cell cycle in these tumor samples is not clear since most of the cells express the antigen in all phases of the cell cycle. On the other hand, there is an association between **HER - 2 / neu** expression and abnormal DNA content suggesting that aneuploid pattern may be biologically related to **overexpression** of the **HER - 2 / neu** gene.

HER - 2 / neu **oncogene expression and DNA ploidy in normal human kidney and** renal **cell** carcinoma .

... **1992** ,
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Descriptors: ***Carcinom** a, **Renal** Cell--genetics--GE; *Kidney --metabolism--ME; *Kidney Neoplasms--genetics--GE; *Oncogene Proteins, Viral--genetics--GE; Aneuploidy; **Carcinoma** , **Renal** Cell--metabolism--ME; DNA--genetics--GE; DNA, Neoplasm--genetics--GE; Flow Cytometry; Gene Expression; Humans...
Gene Symbol: **HER - 2 / neu**

11/3,K,AB/2 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0010763734 BIOSIS NO.: 199799397794
Study of C- erB - 2 **oncoprotein expression in lesions of the uterine cervix**
AUTHOR: Koutselini H; Alexopoulou D; Politi A; Kandaraki C; Noutsou A; Kardiolaka G; Roma M
AUTHOR ADDRESS: Cytopathol. Dep., "Evangelismos" Hosp., Athens, Greece** Greece
JOURNAL: European Journal of Gynaecological Oncology 17 (5): p462-463 1996 **1996**
CONFERENCE/MEETING: IInd National Meeting of the Hellenic Society of Gynaecological Oncology Delphi, Greece October 6-8, 1995; 19951006
ISSN: 0392-2936
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

Study of C- erB - 2 **oncoprotein expression in lesions of the uterine cervix**
1996
DESCRIPTORS:
MISCELLANEOUS TERMS: ...C- **ERB - 2** ONCOPROTEIN...
... **CERVICAL CARCINOMA** ; ...

... **OVEREXPRESSION** ;

11/3,K,AB/3 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0010733047 BIOSIS NO.: 199799367107
Oncogenes and tumor suppressor genes associated with gynecologic malignancies
AUTHOR: Markowska Janina
AUTHOR ADDRESS: Dep. Oncol., Karol Marcinkowski Univ. Med. Sch., Lakowa Str. 1/2, 61-878 Poznan, Poland**Poland
JOURNAL: Central-European Journal of Immunology 21 (3): p211-221 1996
1996
ISSN: 1426-3912
DOCUMENT TYPE: Article; Editorial
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Gene disorders are of critical importance for the development of a malignant tumor. It is suggested that **overexpression** of c-erb-B2 (**HER - 2 / neu**) gene is related to more advanced stages of endometrial cancer, absence of estrogen receptors and worse prognosis. In ovarian cancer, **overexpression** of c-erb-B2 gene similarly coincides with advancement of the disease, worse prognosis and worse response to chemotherapy. Aberrations in structure and expression of INT-2, Ki 67, c-myb, c-myc, c-ras genes can be involved in the course of neoplastic disease. Mutations of c-Ki-ras, p53 genes and HPV type 16 and 18 infection seem to be connected with **cervical carcinoma** .

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DESCRIPTORS:
MISCELLANEOUS TERMS: ... **CERVICAL CARCINOMA** ;

11/3,K,AB/4 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05032741 Genuine Article#: TK584 Number of References: 56
Title: C-ERBB-2 ONCOPROTEIN OVEREXPRESSION **IN UTERINE CERVIX CARCINOMA WITH GLANDULAR DIFFERENTIATION - A FREQUENT EVENT BUT NOT AN INDEPENDENT PROGNOSTIC MARKER BECAUSE IT OCCURS LATE IN THE DISEASE** (Abstract Available)
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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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Corporate Source: IST NAZL TUMORI,DIV ANAT PATHOL & CYTOL,VIA G VENEZIAN 1/I-20133 MILAN//ITALY/; IST NAZL TUMORI,DIV EXPTL ONCOL A/I-20133 MILAN//ITALY/; IST NAZL TUMORI,DIV DIAGNOST ONCOL/I-20133 MILAN//ITALY/ ; IST NAZL TUMORI,OUTPATIENT CLIN/I-20133 MILAN//ITALY/
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...Identifiers--POLYMERASE CHAIN-REACTION; SQUAMOUS-CELL CARCINOMA; TUMOR-SUPPRESSOR GENE; **CERVICAL - CARCINOMA** ; INSITU HYBRIDIZATION; INTRAEPITHELIAL NEOPLASIA; TRANSACTIVATION FUNCTION; MDM2 AMPLIFICATION; UTERINE CERVIX; E6 ONCOPROTEIN
Research Fronts: 93-7675 002 (WILD-TYPE P53; MDM2 GENE; C- **ERB - 2** PROTEIN)
93-1530 001 (WILD-TYPE P53 PROTEIN; TUMOR-SUPPRESSOR GENES; E2F TRANSCRIPTION FACTOR)
93...
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 s frequenc? (5n) (cytolytic or CTL??)
         1555506  FREQUENC?
           26495  CYTOLYTIC
           49480  CTL??
      S1    2003  FREQUENC? (5N) (CYTOLYTIC OR CTL??)
? s (cancer or tumor or malignan?) (5n) (patient?? or subject?? or
individual??)
Processing
         1587540  CANCER
         1653193  TUMOR
          606589  MALIGNAN?
         6536659  PATIENT??
         1678743  SUBJECT??
         1547655  INDIVIDUAL??
      S2  489608  (CANCER OR TUMOR OR MALIGNAN?) (5N) (PATIENT?? OR
                  SUBJECT?? OR INDIVIDUAL??)
? s s1 and s2
            2003  S1
          489608  S2
      S3     170  S1 AND S2
? s peptide
      S4  797559  PEPTIDE
? s s3 and s4
             170  S3
          797559  S4
      S5      94  S3 AND S4
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
      S6      45  RD  (unique items)
? s low
      S7 3325341  LOW
? s s6 and s7
              45  S6
         3325341  S7
      S8      15  S6 AND S7
? t s8/3,k,ab/1-15

 8/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

17996750   PMID: 15756643
  A polyclonal anti-vaccine CD4 T cell response detected with HLA-DP4
multimers in a melanoma patient vaccinated with MAGE-3.DP4- peptide -pulsed
dendritic cells.
  Zhang Yi; Renkvist Nicolina; Sun Zhaojun; Schuler-Thurner Beatrice;
Glaichenhaus Nicolas; Schuler Gerold; Boon Thierry; van der Bruggen Pierre;
Colau Didier
  Ludwig Institute for Cancer Research and Cellular Genetics Unit,
Universite de Louvain, Brussels, Belgium.
  European journal of immunology (Germany)  Apr 2005,  35  (4)  p1066-75,
ISSN 0014-2980   Journal Code: 1273201
  Publishing Model Print
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
```

Record type: MEDLINE; Completed

During the last few years, HLA class I tetramers have been successfully used to demonstrate anti-vaccine CD8 CTL proliferation in **cancer patients** vaccinated with **tumor** antigens. **Frequencies** of **CTL** as **low** as 10(-6) among CD8 cells were observed even in **patients** showing **tumor** regression. Little is known about the role of tumor-antigen-specific CD4 T cells in the context of these anti-vaccine responses. Therefore, we developed a very sensitive approach using fluorescent class-II- **peptide** multimers to detect antigen-specific CD4 T cells in vaccinated **cancer patients** . We produced HLA-DP4 multimers loaded with the MAGE-3(243-258) **peptide** and used them to stain ex vivo PBL from melanoma patients injected with dendritic cells pulsed with several class I and class II tumor antigenic peptides, including the MAGE-3(243-258) **peptide** . The multimer(+) CD4 T cells were sorted and amplified in clonal conditions; specificity was assessed by their ability to secrete IFN-gamma upon contact with the MAGE-3 antigen. We detected frequencies of about 1x10(-6) anti-MAGE-3.DP4 cells among CD4 cells. A detailed analysis of one patient showed an anti-MAGE-3.DP4 CD4 T cell amplification of at least 3000-fold upon immunization. TCR analysis of the clones from this patient demonstrated a polyclonal response against the MAGE-3 **peptide** .

... **response detected with HLA-DP4 multimers in a melanoma patient vaccinated with MAGE-3.DP4-** peptide **-pulsed dendritic cells.**

... class I tetramers have been successfully used to demonstrate anti-vaccine CD8 CTL proliferation in **cancer patients** vaccinated with **tumor** antigens. **Frequencies** of **CTL** as **low** as 10(-6) among CD8 cells were observed even in **patients** showing **tumor** regression. Little is known about the role of tumor-antigen-specific CD4 T cells in...

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... analysis of the clones from this patient demonstrated a polyclonal response against the MAGE-3 **peptide** .

...Descriptors: Cells--immunology--IM; *HLA-DP Antigens--immunology--IM; *Melanoma--immunology--IM; *Neoplasm Proteins--immunology--IM; * **Peptide** Fragments--immunology--IM...; HLA-DP Antigens--metabolism--ME; Humans; Immunotherapy, Adoptive; Melanoma--therapy--TH; Neoplasm Proteins --metabolism--ME; **Peptide** Fragments--metabolism--ME; Vaccination

...Chemical Name: Cancer Vaccines; Epitopes, T-Lymphocyte; HLA-DP Antigens; HLA-DP4; MAGEA3 protein, human; Neoplasm Proteins; **Peptide** Fragments; Biotin

8/3,K,AB/2 **(Item 2** from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15487635 PMID: 15452345

Correlation between tumor regression and T cell responses in melanoma

patients vaccinated with a MAGE antigen.

Lonchay Christophe; van der Bruggen Pierre; Connerotte Thierry; Hanagiri Takeshi; Coulie Pierre; Colau Didier; Lucas Sophie; Van Pel Aline; Thielemans Kris; van Baren Nicolas; Boon Thierry

Ludwig Institute for Cancer Research, Brussels Branch of Human Cell Genetics, Universite de Louvain, 74 Avenue Hippocrate, UCL 7459, B-1200 Brussels, Belgium.

Proceedings of the National Academy of Sciences of the United States of America (United States) Oct 5 2004, 101 Suppl 2 p14631-8, ISSN 0027-8424 Journal Code: 7505876

Publishing Model Print-Electronic

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The cancer-germline gene MAGE-3 codes for tumor-specific antigens recognized on many tumors by T lymphocytes. A MAGE-3 antigen presented by HLA-A1 has been used in several vaccination trials on metastatic melanoma patients. Only a small minority of **patients** have shown evidence of **tumor** regression. Attempts to correlate the tumor rejections with the cytotoxic T lymphocyte (CTL) response against the vaccine have been hampered by the **low** level of these responses. In noncancerous individuals, the frequency of the T cell precursors against antigen MAGE-3.A1 is approximately 4 x 10(-7) CD8 T cells. The diversity of the T cell receptor repertoire of these anti-MAGE-3.A1 precursors was analyzed in one individual. The results indicate that it is very likely that the repertoire comprises >100 clonotypes. On this basis, it is possible to use not only the **frequency** of **CTL** precursors in the blood but also the presence of dominant clonotypes to ascertain in patients the existence of anti-MAGE-3.A1 responses as **low** as 10(-6) of CD8. With this approach, we observed a correlation between tumor regression and anti-MAGE-3.A1 CTL responses in patients vaccinated with a recombinant virus encoding the antigen and also in patients vaccinated with **peptide** -pulsed dendritic cells. In contrast, for **patients** showing **tumor** regression after vaccination with **peptide** alone, CTL responses were almost never observed. It is possible that even those CTL responses that are below our present detection level can trigger a sequence of events that leads to tumor regression.

... been used in several vaccination trials on metastatic melanoma patients. Only a small minority of **patients** have shown evidence of **tumor** regression. Attempts to correlate the tumor rejections with the cytotoxic T lymphocyte (CTL) response against the vaccine have been hampered by the **low** level of these responses. In noncancerous individuals, the frequency of the T cell precursors against...

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8/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15023962 PMID: 14568971

Monoclonal anti-MAGE-3 CTL responses in melanoma patients **displaying** tumor **regression after vaccination with a recombinant canarypox virus.**

Karanikas Vaios; Lurquin Christophe; Colau Didier; van Baren Nicolas; De Smet Charles; Lethe Bernard; Connerotte Thierry; Corbiere Veronique; Demoitie Marie-Ange; Lienard Danielle; Dreno Brigitte; Velu Thierry; Boon Thierry; Coulie Pierre G

Cellular Genetics Unit, Institute of Cellular Pathology, Universite de Louvain, Brussels, Belgium.

Journal of immunology (Baltimore, Md. - 1950) (United States) Nov 1 2003, 171 (9) p4898-904, ISSN 0022-1767 Journal Code: 2985117R

Publishing Model Print

Document type: Case Reports; Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

We have analyzed the T cell responses of HLA-A1 metastatic melanoma patients with detectable disease, following vaccination with a recombinant ALVAC virus, which bears short MAGE-1 and MAGE-3 sequences coding for antigenic peptides presented by HLA-A1. To evaluate the anti-MAGE CTL responses, we resorted to antigenic stimulation of blood lymphocytes under limiting dilution conditions, followed by tetramer analysis and cloning of the tetramer-positive cells. The clones were tested for their specific lytic ability and their TCR sequences were obtained. Four **patients** who showed **tumor** regression were analyzed, and an anti-MAGE-3.A1 CTL response was observed in three of these patients. Postvaccination **frequencies** of anti-MAGE-3.A1 **CTL** were 3 x 10(-6), 3 x 10(-3), and 3 x 10(-7) of the blood CD8 T cells, respectively. These three responses were monoclonal. No anti-MAGE-1.A1 CTL response was observed. These results indicate that, like **peptide** immunization, ALVAC immunization produces monoclonal responses. They also suggest that **low** -level antivaccine CTL responses can initiate a tumor regression process. Taken together, our analysis of anti-MAGE-3.A1 T cell responses following **peptide** or ALVAC vaccination shows a degree of correlation between CTL response and tumor regression, but firm conclusions will require larger numbers.

Monoclonal anti-MAGE-3 CTL responses in melanoma patients **displaying** tumor **regression after vaccination with a recombinant** canarypox virus.

... clones were tested for their specific lytic ability and their TCR sequences were obtained. Four **patients** who showed **tumor** regression were analyzed, and an anti-MAGE-3.A1 CTL response was observed in three of these patients. Postvaccination **frequencies** of anti-MAGE-3.A1 **CTL** were 3 x 10(-6), 3 x 10(-3), and 3 x 10(-7) of...

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8/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14658284 PMID: 12411306

Generating CTLs against the subdominant Epstein-Barr virus LMP1 antigen for the adoptive immunotherapy of EBV-associated malignancies.

Gottschalk Stephen; Edwards Oliver L; Sili Uluhan; Huls M Helen; Goltsova Tatiana; Davis Alan R; Heslop Helen E; Rooney Cliona M

Center for Cell and Gene Therapy, Texas Children's Cancer Center, Departments of Pediatrics, Medicine, and Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030, USA. smg@bcm.tmc.edu

Blood (United States) Mar 1 2003, 101 (5) p1905-12, ISSN 0006-4971 Journal Code: 7603509

Contract/Grant No.: CA-16672; CA; NCI; R01 CA61384; CA; NCI; R01 CA74126; CA; NCI

Publishing Model Print-Electronic

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The Epstein-Barr virus (EBV)-encoded LMP1 protein is expressed in EBV-positive Hodgkin disease and is a potential target for cytotoxic T-lymphocyte (CTL) therapy. However, the LMP1-specific **CTL frequency** is **low** , and so far the generation of LMP1-specific CTLs has required T-cell cloning. The toxicity of LMP1 has prevented the use of dendritic cells (DCs) for CTL stimulation, and we reasoned that an inactive, nontoxic LMP1 mutant (DeltaLMP1) could be expressed in DCs and would enable the activation and expansion of polyclonal LMP1-specific CTLs. Recombinant adenoviral vectors expressing LMP1 or DeltaLMP1 were tested for their ability to transduce DCs. LMP1 expression was toxic within 48 hours whereas high levels of DeltaLMP1 expression were achieved with minimal toxicity. DeltaLMP1-expressing DCs were able to reactivate and expand LMP1-specific CTLs from 3 healthy EBV-seropositive donors. LMP1-specific T cells were detected by interferon-gamma (IFN-gamma) enzyme-linked immunospot assay (ELISPOT) assays using the HLA-A2-restricted LMP1 **peptide** , YLQQNWWTL (YLQ). YLQ-specific T cells were undetectable (less than 0.001%) in donor peripheral blood mononuclear cells (PBMCs); however, after stimulation the frequency increased to 0.5% to 3.8%. Lysis of autologous target cells by CTLs was dependent on the level of LMP1 expression. In contrast, the **frequency** of YLQ-specific **CTLs** in EBV-specific CTLs reactivated and expanded using lymphoblastoid cell lines was **low** and no LMP1-specific cytotoxic activity was observed. Thus, DeltaLMP1 expression in DCs is nontoxic and enables the generation of LMP1-specific CTLs for future adoptive immunotherapy protocols for **patients** with LMP1-positive **malignancies** such as EBV-positive Hodgkin disease. Targeting LMP1 in these malignancies may improve the efficacy of current adoptive immunotherapy approaches.

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... gamma (IFN-gamma) enzyme-linked immunospot assay (ELISPOT) assays using the HLA-A2-restricted LMP1 **peptide** , YLQQNWWTL (YLQ). YLQ-specific T cells were undetectable (less than 0.001%) in donor peripheral...

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8/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14167298 PMID: 11955649

Functional detection of epithelial cell adhesion molecule specific cytotoxic T lymphocytes in patients **with lung** cancer , **colorectal** cancer **and in healthy donors.**

Trojan Andreas; Tun-Kyi Adrian; Odermatt Bernhard; Nestle Frank O; Stahel Rolf A

Division of Oncology, Department of Internal Medicine, University Hospital Zurich, Ramistrasse 100, 8091, Switzerland. andreas.trojan@dim.usz.ch

Lung cancer (Amsterdam, Netherlands) (Ireland) May 2002, 36 (2) p151-8, ISSN 0169-5002 Journal Code: 8800805

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Epithelial cell adhesion molecule (Ep-CAM) derived antigenic peptides have been identified that can be recognized by cytotoxic T lymphocytes (CTL) in a major histocompatibility complex (MHC) class I restricted fashion. Thus, altered expression of Ep-CAM in a variety of human tumors might render a potential target for T cell mediated therapy. We have examined, whether the novel HLA-A*0201 restricted **peptide** ILYENNVIT (184-192) corresponding to Ep-CAM and one heteroclitic modified variant **peptide** previously demonstrated to be immunogenic in the human system can elicit antigen specific CTL responses in HLA-A2 positive patients with history of Ep-CAM expressing cancer of lung and colon. Specific CTL recognition of T2 target cells pulsed with the native **peptide** as well as of the lung cancer cell line A549 indicates that an appropriate T cell repertoire can be expanded from peripheral blood from patients in clinical remission and with advanced cancer. Despite an overall **low frequency** , **peptide** specific precursor **CTLs** could be readily expanded from peripheral blood from 6/8 patients that were diagnosed previously with Ep-CAM expressing lung **cancer** and 4/8 control **individuals** (2/5 healthy donors and 2/3 colon **cancer patients**). CTLs from three of five lung **cancer patients** tested also lyzed the HLA-A2(+) and Ep-CAM expressing lung cancer cell line A549. We did not detect an increased frequency of pCTLs after peripheral blood monocytes (PBMCs) were stimulated with the heteroclitic compound **peptide** . The results of our study indicate that Ep-CAM specific precursor CTL can be expanded in vitro and a specific T cell response against this epitope can be elicited in **patients** at various stages of lung **cancer** .

Functional detection of epithelial cell adhesion molecule specific cytotoxic T lymphocytes in patients **with lung** cancer , **colorectal** cancer and in healthy donors.

... for T cell mediated therapy. We have examined, whether the novel HLA-A*0201 restricted **peptide** ILYENNVIT (184-192) corresponding to Ep-CAM and one heteroclitic modified variant **peptide** previously demonstrated to be immunogenic in the human system can elicit antigen specific CTL responses...

... of lung and colon. Specific CTL recognition of T2 target cells pulsed with the native **peptide** as well as of the lung cancer cell line A549 indicates that an appropriate T...

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...; immunology--IM; Epitopes, T-Lymphocyte--immunology--IM; HLA-A2 Antigen--immunology--IM; Humans; Middle Aged; **Peptide** Fragments --immunology--IM; Tumor Cells, Cultured; Tumor Markers, Biological --immunology--IM

Chemical Name: Antigens, Neoplasm; Cell Adhesion Molecules; Epitopes, T-Lymphocyte; HLA-A2 Antigen; **Peptide** Fragments; Tumor Markers, Biological; tumor-associated antigen GA733

8/3,K,AB/6 (Item 6 from file: 155)

13712521 PMID: 11359807

Three different vaccines based on the 140-amino acid MUC1 peptide **with seven tandemly repeated tumor-specific epitopes elicit distinct immune effector mechanisms in wild-type versus MUC1-transgenic mice with different potential for tumor rejection.**

Soares M M; Mehta V; Finn O J

Immunology Program and Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine, Pittsburgh PA 15261, USA.

Journal of immunology (Baltimore, Md. - 1950) (United States) Jun 1 2001, 166 (11) p6555-63, ISSN 0022-1767 Journal Code: 2985117R

Contract/Grant No.: 5RO1 CA56103; CA; NCI

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Low - frequency CTL and **low** -titer IgM responses against tumor-associated Ag MUC1 are present in **cancer patients** but do not prevent **cancer** growth. Boosting MUC1-specific immunity with vaccines, especially effector mechanisms responsible for tumor rejection, is an important goal. We studied immunogenicity, tumor rejection potential, and safety of three vaccines: 1) MUC1 **peptide** admixed with murine GM-CSF as

an adjuvant; 2) MUC1 **peptide** admixed with adjuvant SB-AS2; and 3) MUC1 **peptide** -pulsed dendritic cells (DC). We examined the qualitative and quantitative differences in humoral and T cell-mediated MUC1-specific immunity elicited in human MUC1-transgenic (Tg) mice compared with wild-type (WT) mice. Adjuvant-based vaccines induced MUC1-specific Abs but failed to stimulate MUC1-specific T cells. MUC1 **peptide** with GM-CSF induced IgG1 and IgG2b in WT mice but only IgM in MUC1-Tg mice. MUC1 **peptide** with SB-AS2 induced high-titer IgG1, IgG2b, and IgG3 Abs in both WT and MUC1-Tg mice. Induction of IgG responses was T cell independent and did not have any effect on tumor growth. MUC1 **peptide** -loaded DC induced only T cell immunity. If injected together with soluble **peptide** , the DC vaccine also triggered Ab production. Importantly, the DC vaccine elicited tumor rejection responses in both WT and MUC1-Tg mice. These responses correlated with the induction of MUC1-specific CD4+ and CD8+ T cells in WT mice, but only CD8(+) T cells in MUC1-Tg mice. Even though MUC1-specific CD4+ T cell tolerance was not broken, the capacity of MUC1-Tg mice to reject tumor was not compromised.

Three different vaccines based on the 140-amino acid MUC1 peptide **with seven tandemly repeated tumor-specific epitopes** elicit distinct immune **effector mechanisms in wild-type...**

Low - frequency CTL and **low** -titer IgM responses against tumor-associated Ag MUC1 are present in **cancer patients** but do not prevent **cancer** growth. Boosting MUC1-specific immunity with vaccines, especially effector mechanisms responsible for tumor rejection, is...

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... responses was T cell independent and did not have any effect on tumor growth. MUC1 **peptide** -loaded DC induced only T cell immunity. If injected together with soluble **peptide** , the DC vaccine also triggered Ab production. Importantly, the DC vaccine elicited tumor rejection responses ...

...Descriptors: IM; *Epitopes, T-Lymphocyte--immunology--IM; *Graft Rejection--immunology--IM; *Lymphoma, T-Cell--immunology--IM; * **Peptide** Fragments--immunology--IM...; GE; Lymphoma, T-Cell--therapy--TH; Mice; Mice, Inbred C57BL; Mice, Transgenic; Molecular Sequence Data; **Peptide** Fragments--administration and dosage--AD; **Peptide** Fragments--genetics --GE; Repetitive Sequences, Amino Acid; Tumor Cells, Cultured

...Chemical Name: CA-15-3 Antigen; Cancer Vaccines; Epitopes, T-Lymphocyte; Immunoglobulin G; Immunoglobulin Isotypes; MUC1 mucin **peptide** ; **Peptide** Fragments; Interferon Type II

8/3,K,AB/7 (Item 7 from file: 155)

13508444 PMID: 10477550

An expanded peripheral T cell population to a cytotoxic T lymphocyte (CTL)-defined, melanocyte-specific antigen in metastatic melanoma patients impacts on generation of peptide **-specific CTLs but does not overcome tumor escape from immune surveillance in metastatic lesions.**

Anichini A; Molla A; Mortarini R; Tragni G; Bersani I; Di Nicola M; Gianni A M; Pilotti S; Dunbar R; Cerundolo V; Parmiani G

Department of Experimental Oncology Human Tumor Immunobiology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, 20133 Milan, Italy. Anichini@istitutotumori.mi.it

Journal of experimental medicine (UNITED STATES) Sep 6 1999, 190 (5) p651-67, ISSN 0022-1007 Journal Code: 2985109R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

It is not known if immune response to T cell-defined human histocompatibility leukocyte antigen (HLA) class I-restricted melanoma antigens leads to an expanded peripheral pool of T cells in all patients, affects cytotoxic T lymphocyte (CTL) generation, and correlates with anti-tumor response in metastatic lesions. To this end, a limiting dilution analysis technique was developed that allowed us to evaluate the same frequency of **peptide** -specific T cells as by staining T cells with HLA- **peptide** tetrameric complexes. In four out of nine patients, Melan-A/Mart-1(27-35)-specific CTL precursors (CTLp) were >/=1/2,000 peripheral blood lymphocytes and found mostly or only in the CD45RO(+) memory T cell subset. In the remaining five patients, a **low** (<1/40,000) **peptide** -specific **CTLp frequency** was measured, and the precursors were only in the CD45RA(+) naive T cell subset. Evaluation of **CTL** effector **frequency** after bulk culture indicated that **peptide** -specific CTLs could be activated in all patients by using professional antigen-presenting cells as dendritic cells, but **CTLp frequency** determined the kinetics of generation of specificity and the final number of effectors as evaluated by both limiting dilution analysis and staining with HLA-A*0201-Melan-A/Mart-1 tetrameric complexes. Immunohistochemical analysis of 26 neoplastic lesions from the nine **patients** indicated absence of **tumor** regression in most instances, even in patients with an expanded peripheral T cell pool to Melan-A/Mart-1 and whose neoplastic lesions contained a high frequency of tetramer-positive Melan-A/Mart-1-specific T cells. Furthermore, frequent lack of a "brisk" or "nonbrisk" CD3(+)CD8(+) T cell infiltrate or reduced/absent Melan-A/Mart-1 expression in several lesions and lack of HLA class I antigens were found in some instances. Thus, expansion of peripheral immune repertoire to Melan-A/Mart-1 takes place in some metastatic patients and leads to enhanced CTL induction after antigen-presenting cell-mediated selection, but, in most metastatic lesions, it does not overcome tumor escape from immune surveillance.

...**T lymphocyte (CTL)-defined, melanocyte-specific antigen in metastatic melanoma patients impacts on generation of** peptide **-specific CTLs but does not overcome tumor escape from immune surveillance in metastatic lesions.**

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8/3,K,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13317844 PMID: 10093034

Quantitation of T-cell receptor frequencies by competitive PCR: generation and evaluation of novel TCR subfamily and clone specific competitors.

McKee M D; Clay T M; Rosenberg S A; Nishimura M I
Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.

Journal of immunotherapy (Hagerstown, Md. - 1997) (UNITED STATES) Mar 1999, 22 (2) p93-102, ISSN 1524-9557 Journal Code: 9706083
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

T cell receptor (TCR) V gene usage has been used to characterize the immune response to bacteria, viruses, allografts, self antigens, tumor antigens, and superantigens. Sensitive methods to detect changes in the frequency of TCR subfamilies or clonotypes might be useful in evaluating the efficacy of vaccines against infectious agents, immunotherapy treatments for **cancer patients** , or the status of autoimmune diseases. Two HLA-A2 restricted CTL clones expressing BV17 were isolated from a tumor infiltrating lymphocytes (TIL) culture of a patient with metastatic melanoma. One clone recognized the MART-1(27-35) **peptide** and the other clone recognized the gp100(209-217) **peptide** . The **frequency** of each of these **CTL** clones in an expanding TIL culture was measured using a novel competitive RT-PCR (cRT-PCR) strategy. cRT-PCR uses a single primer pair to amplify template cDNA simultaneously with a modified DNA competitor molecule. A rapid two-step PCR technique followed by a single cloning step was used to generate a TCR BV17 subfamily specific competitor or competitors specific for the MART-1(27-35) reactive CTL clone (CO-41) and the gp100(209-217) reactive CTL clone (CO-4). Each competitor contained a segment of the TCR BC region that served as an internal reference standard. Using the BV17 competitor we were able to accurately and reproducibly measure cDNA templates at a frequency as **low** as 1/100,000 using cDNA samples of known TCRBV subfamily composition. This competitor was used to monitor the frequency of BV17 expressing T cells in the TIL and PMBC of a patient with metastatic melanoma. We determined that the frequency of BV17 expressing T cells increased from 4.5% of the culture on day 35 to 60.7% of the culture on day 58. Expansion of the BV17 subfamily was due predominantly to the expansion of the CO-4 clone. This method can be used to meaningfully quantify the precursor frequency of T cell mRNA in prepared samples via TCR subfamily or TCR sequence specific primers.

... might be useful in evaluating the efficacy of vaccines against infectious agents, immunotherapy treatments for **cancer patients** , or the status of autoimmune diseases. Two HLA-A2 restricted CTL clones expressing BV17 were...

... culture of a patient with metastatic melanoma. One clone recognized the MART-1(27-35) **peptide** and the other clone recognized the gp100(209-217) **peptide** . The **frequency** of each of these **CTL** clones in an expanding TIL culture was measured using a novel competitive RT-PCR (cRT...

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8/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12955546 PMID: 10910069

Peripheral burst of tumor-specific cytotoxic T lymphocytes and infiltration of metastatic lesions by memory CD8+ T cells in melanoma patients receiving interleukin 12.

Mortarini R; Borri A; Tragni G; Bersani I; Vegetti C; Bajetta E; Pilotti S; Cerundolo V; Anichini A

Department of Experimental Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

Cancer research (UNITED STATES) Jul 1 2000, 60 (13) p3559-68, ISSN 0008-5472 Journal Code: 2984705R

Publishing Model Print

Document type: Clinical Trial; Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Systemic effects on T-cell-mediated antitumor immunity, on expression of T-cell adhesion/homing receptors, and on the promotion of T-cell infiltration of neoplastic tissue may represent key steps for the efficacy of immunological therapies of cancer. In this study, we investigated whether these processes can be promoted by s.c. administration of **low** -dose (0.5 microg/kg) recombinant human interleukin-12 (rHuIL-12) to metastatic melanoma patients. A striking burst of HLA-restricted CTL precursors (CTLp) directed to autologous tumor was documented in peripheral blood by a high-efficiency limiting dilution analysis technique within a few days after rHuIL-12 injection. A similar burst in peripheral **CTLp frequency** was observed even when looking at response to a single tumor-derived **peptide** , as documented by an increase in Melan-A/Mart-1(27-35)-specific CTLp in two HLA-A*0201+ patients by limiting dilution analysis and by staining peripheral blood lymphocytes (PBLs) with HLA-A*0201-melanoma antigen-A/melanoma antigen recognized by T cells (Melan-A/Mart)-1 tetrameric complexes. The CTLp burst was associated, in PBLs, with enhanced expression of T-cell adhesion/homing receptors CD11a/CD18, CD49d, CD44, and with increased proportion of cutaneous lymphocyte antigen (CLA)-positive T cells. This was matched by a marked increase, in serum, of soluble forms of the endothelial cell adhesion molecules E-selectin, vascular cell adhesion molecules (VCAM)-1 and intercellular adhesion molecules (ICAM)-1. Infiltration of neoplastic tissue by CDS+ T cells with a memory and cytolytic phenotype was found by immunohistochemistry in eight of eight posttreatment metastatic lesions but

not in five of five pretreatment metastatic lesions from three **patients** . Increased **tumor** necrosis and/or fibrosis were also found in several posttherapy lesions of two of three patients in comparison with pretherapy metastases. These results provide the first evidence that rHuIL-12 can boost the **frequency** of circulating antitumor **CTLp** in **tumor patients** , enhances expression of ligand receptor pairs contributing to the lymphocyte function-associated antigen-1/ICAM-1, very late antigen-4/VCAM-1, and CLA/E-selectin adhesion pathways, and promotes infiltration of neoplastic lesions by CD8+ memory T cells in a clinical setting.

...this study, we investigated whether these processes can be promoted by s.c. administration of **low** -dose (0.5 microg/kg) recombinant human interleukin-12 (rHuIL-12) to metastatic melanoma patients...

...analysis technique within a few days after rHuIL-12 injection. A similar burst in peripheral **CTLp frequency** was observed even when looking at response to a single tumor-derived **peptide** , as documented by an increase in Melan-A/Mart-1(27-35)-specific CTLp in...

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... with pretherapy metastases. These results provide the first evidence that rHuIL-12 can boost the **frequency** of circulating antitumor **CTLp** in **tumor patients** , enhances expression of ligand receptor pairs contributing to the lymphocyte function-associated antigen-1/ICAM...

8/3,K,AB/10 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0014794214 BIOSIS NO.: 200400161555
High frequency of functionally active tumor antigen-specific T cells in a patient with progressive LMP2 deficient tumor .
AUTHOR: Mackensen Andreas (Reprint); Zippelius Alfred; Pittet Mikael J; Vogl Sandra (Reprint); Laumer Monika (Reprint); Heymann Jana (Reprint); Rehli Michael (Reprint); Seliger Barbara; Andreesen Reinhard (Reprint); Romero Pedro; Meidenbauer Norbert (Reprint)
AUTHOR ADDRESS: Dept. of Hematology and Oncology, University of Regensburg, Regensburg, Germany**Germany
JOURNAL: Blood 102 (11): p52b November 16, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Tumor-reactive T cells have been demonstrated to play an important role in cancer immunosurveillance. Applying the multimer technology, previous studies demonstrated that CD8+ cytotoxic T lymphocytes (CTL) directed against the melanocyte differentiation antigen

Melan-A can be frequently found in melanoma patients. Here we report an unexpected high **frequency** of circulating Melan-A specific **CTL** of more than 14% of the total CD8+ T cells. To best of our knowledge, this is the highest reported frequency of circulating CD8+ T cells directed against a single tumor-associated antigen (TAA). Despite the presence of this high number of TAA-specific T cells, the patient had rapidly progressing lymph node (LN) melastases. Since selective anergy of TAA-specific T cells has been proposed as a possible immune escape mechanism in malignant melanoma, we thoroughly assessed phenotype and effector function of Melan-A-specific CTL in this patient. Melan-A specific T cells consisted of memory effector (CD45RA-/CCR7-) and terminally differentiated effector T cells (CD45RA+/CCR7-). Functional characterization of Melan-A specific CTL demonstrated specific secretion of IFN-gamma upon antigenic stimulation and killing of Melan-A-pulsed target cells as well as of allogeneic HLA-A2+ Melan-A+ tumor cells. Furthermore, ex vivo analysis of the metastatic LN revealed the presence of functionally active Melan-A-specific **CTL** in a high **frequency** comparable to the peripheral blood. However, the autologous Melan-A-specific CD8+ T cells as well as an allogeneic HLA-A2-matched Melan-A-specific CTL line failed to kill the **patient** 's **tumor** cells isolated from metastatic LN. Loading of the tumor with the Melan-A **peptide** completely reversed the resistance to killing, suggesting impaired function of the antigen processing and presentation pathway. Downregulation of HLA class I or mutation of the antigenic **peptide** as immune escape mechanisms could be excluded. Detailed analysis of the HLA class I antigen processing machinery revealed no alterations in MHC antigens, TAP, tapasin and the **low** molecular weight protein (LMP)7 expression, but LMP2 deficiency in the primary **tumor** cells of the **patient** , which may explain (i) the lack of killing of autologous tumor cells and (ii) the progressive disease in the melanoma patient. Overall, this is the first report of an extremely high **frequency** of TAA-specific **CTL** in the peripheral blood and tumor-infiltrating LN that exhibit competent T cell effector functions, but fail to lyse the autologous tumor cells. Lack of tumor killing can be explained by alterations of the multicatalytic proteasome complex which might affect the quantity and quality of generated T cell epitopes. This case highlights, that immunotherapeutic approaches should not only focus on the induction of a robust anti-tumor immune response, but also have to target tumor immune escape mechanisms.

High frequency of functionally active tumor antigen-specific T cells in a patient **with progressive LMP2 deficient** tumor .

...ABSTRACT: Melan-A can be frequently found in melanoma patients. Here we report an unexpected high **frequency** of circulating Melan-A specific **CTL** of more than 14% of the total CD8+ T cells. To best of our knowledge ...

...vivo analysis of the metastatic LN revealed the presence of functionally active Melan-A-specific **CTL** in a high **frequency** comparable to the peripheral blood. However, the autologous Melan-A-specific CD8+ T cells as...

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8/3,K,AB/11 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0014781988 BIOSIS NO.: 200400148649
Detectable frequencies **of cytotoxic T cells** (CTL) **recognizing** peptide **epitopes of CD19 and CD20 occur in healthy individuals and in** patients **with B cell** malignancies .
AUTHOR: Grube Matthias (Reprint); Rezvani Katayoun (Reprint); Wiestner Adrian; Fujiwara Hiroshi (Reprint); Sconocchia Giuseppe (Reprint); Melenhorst Jan J (Reprint); Hensel Nancy (Reprint); Barrett John A (Reprint)
AUTHOR ADDRESS: Hematology Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA**USA
JOURNAL: Blood 102 (11): p894a November 16, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The generation of tissue specific autoimmune responses represents an important approach in cancer immunotherapy. To investigate potential immunotherapeutic strategies in B lymphocytic malignancies, we set out to determine, whether cytotoxic T lymphocytes (CTL) recognizing CD19 and CD20 epitopes can be detected in healthy individuals and patients. We identified three peptides (CD19p, CD20a and CD20b) binding to HLA-A*0201 and determined their ligation strength to MHC-molecules by the T2-binding assay. To detect antigen specific T-cells, we incubated CD8+ selected T-cells with antigen-presenting-cells (C1R-A2) pulsed or not pulsed with the test peptides. We used quantitative real time PCR to measure IFN-gamma mRNA expression for the detection of **peptide** specific CTL in 23 healthy individuals and 28 patients (18 CLL, 7 follicular lymphoma, 2 ALL and 1 NHL). A **peptide** stimulation index (SI, test **peptide** reactivity/no **peptide** reactivity) of 2 or greater was considered a positive response. 1/21 (5%) healthy individuals had a CD8+ T cell response to CD19p (SI 2.6), 3/14 (21%) had a response to CD20a (SI 2.0-3.5) and 3/23 (13%) to CD20b (SI 2.2-2.3) respectively. 6/17 (35%) patients with CLL and 1/10 (10%) **patients** with other B-cell **malignancies** had CD8+ T cells recognizing CD19p with SI between 2.1-7.1 and 2.3 respectively. 7/15 (47%) patients with CLL had a response to CD20a (SI 2.3-3.0) and 3/16 (19%) to CD20b (SI 2.3-3.7). No T cell reactivity to CD20 peptides was detected in **patients** with B-cell

malignancies other than CLL. CD19p-specific CTL from three patients were expanded over 4 weeks using **peptide** -pulsed CD40-activated B-cells in medium containing 10U/ml IL-2 and 10ng/ml IL-7. The T cells showed HLA-A*0201-restricted target recognition and were lytic for **peptide** -loaded APC but not for malignant or unpulsed B cells. Our data suggest that (1) CTL recognizing CD19 and CD20 derived peptides exist in normal healthy individuals and in **patients** with B-cell **malignancies** with an increase in CLL (2) **peptide** specific CTL can be expanded by restimulation with synthetic **peptide** (3) specific T cells are **low** avidity and require high doses of **peptide** for activation. Strategies to increase T cell avidity would be necessary for T cell immunotherapeutic approaches using the peptides studied.

Detectable frequencies **of cytotoxic T cells** (CTL) **recognizing** peptide **epitopes of** CD19 and CD20 occur in healthy individuals and in patients **with B cell** malignancies .

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DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...expression, **peptide** epitope...

...expression, **peptide** epitope...

8/3,K,AB/12 (Item 3 from file: 55)

DIALOG(R)File 55:Biosis Previews(R)

0014409973 BIOSIS NO.: 200300368692

A Highly Sensitive RT-PCR Assay for Interferon-gamma Identifies Multiple Circulating Low **Frequency CD8+ T Cells Recognizing Tumor Peptides PR1, WT1 and BCR-ABL in Normal Individuals, CML Patients and Stem Cell**

Transplant (SCT) Recipients.

AUTHOR: Rezvani K (Reprint); Grube M (Reprint); Hensel N (Reprint); Fujiwara H (Reprint); Sconocchia G (Reprint); Barrett J (Reprint)
AUTHOR ADDRESS: National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD, USA**USA
JOURNAL: Blood 100 (11): pAbstract No. 5208 November 16, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Donor-derived T cells responding to tumor antigens circulate after SCT and are associated with leukemic remission. Healthy HLA-A2 positive individuals have **low frequencies** of **CTL** recognizing overexpressed tumor antigens e.g. PR1 a **peptide** from the primary granule protein, proteinase-3 and WT1, a transcription factor overexpressed in many acute leukemias, CML and solid tumors. The frequency of such antigen-specific T cells is **low** and often at the limits of detection with current techniques. We developed a sensitive functional assay to directly measure activity of CTLs against potential tumor antigens from PBMC from normal donors and patients with CML. As candidate antigens we chose HLA A*0201 binding peptides from the bcr-abl and abl-bcr junctions, PR3, PRAME, WT1 and CD66c. We developed a quantitative RT-PCR measurement of **peptide** -specific IFN-gamma production by CD8+ T cells. Total RNA was extracted from 1x106/ml **peptide** stimulated CD8+ T cells and reverse transcribed into cDNA. Measurement of IFN-gamma gene expression was performed using an ABI prism 7900 Sequence Detection System. Primers and TaqMan probes were designed to span exon-intron junctions to prevent amplification of genomic DNA. IFN-gamma was quantified relative to the expression of the CD8 gene. HLA-A*0201, CMV seropositive and negative healthy volunteers and CML patients pre and post SCT were apheresed. CD8+ T cells were positively selected and used as effector cells. T2 cells were used as APC, exposed for 2h to 0.1-10muM candidate tumor **peptide** and as a control the HLA A*0201 restricted CMV **peptide** pp65495-503. Optimum IFN- gamma mRNA production occurred at 3-6 hrs. The assay is extremely sensitive and reproducible both in repeat assays of the same specimen and in repetitive testing of the same individual. Negative controls including HLA A2 negative individuals and CMV negative A2 positive individuals are consistently negative. By comparing the frequency by tetramer analysis and RT-PCR of increasing dilutions of CMV pp65 and PR1 specific CD8 cells, RT-PCR was found to be 1-2 logs more sensitive, detecting antigen-specific T cells at frequencies in the order of 1:10,000 to 1:100,000. A number of normal donors showed a substantial increase in IFN- gamma production upon stimulation of their CTLs with PR1 and WT1 pulsed T2 cells. Of 12 normal donors tested 3 had PR1 specific activity, 4 had responses to WT1and 1had a response to CD66c. Stimulation indices (SI) varied between 3-420. No response was detected against bcr-abl **peptide** . Six of 10 CML patients pre- SCT had large responses (SI: 3-404) to multiple tumor peptides including PR1, WT1 and bcr-abl predominantly elicited only by high antigen concentrations, suggesting the presence of an autologous **tumor** response. Two **patients** in karyotypic but not molecular remission of CML were studied 100 and 180 days post SCT. Both showed high SI (up to 9643) against **low** concentrations of PR1 and WT1

peptides and one to bcr-abl. These results suggest that **low** frequencies of autoreactive T cells recognizing multiple **tumor** antigens exist in normal **individuals** and patients with leukemia. Post transplant finding suggests that GVL effects may be diverse - exerted by expansion of multiple clones of higher affinity T cells recognizing a variety of tumor antigens. We plan to use this technique to screen donors for leukemia-specific CTL, detect new candidate tumor antigens and study GVL response.

A Highly Sensitive RT-PCR Assay for Interferon-gamma Identifies Multiple Circulating Low **Frequency CD8+ T Cells Recognizing Tumor Peptides PR1, WT1 and BCR-ABL in Normal Individuals...**

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DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: ...tumor **peptide** ; ...

...tumor **peptide** ;

8/3,K,AB/13 (Item 4 from file: 55)

0013103769 BIOSIS NO.: 200100275608

Tumor rejection and long term protection in MUC1 transgenic mice is mediated by MUC1-specific, IFN-gamma producing CD8+ T cells, in the absence of CD4+ T cells

AUTHOR: Soares M Melina (Reprint); Finn Olivera J (Reprint)
AUTHOR ADDRESS: University of Pittsburgh, Terrace and Desoto Sts, Pittsburgh, PA, 15261, USA**USA
JOURNAL: FASEB Journal 15 (4): pA656 March 7, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001; 20010331
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: MUC1 is a tumor antigen expressed by breast, pancreatic, colon, lung and ovarian adenocarcinomas. In **cancer patients** , it is possible to detect **low** titer MUC1-specific IgM antibody and **low frequency CTL** responses. There are no detectable MUC1-specific CD4+ T helper responses which suggests tolerance to this antigen and might account in part for the inability of these patients to recover from the disease. We have investigated the qualitative and quantitative differences in MUC1-specific responses following vaccination of conventional mice (wherein human MUC1 is a foreign antigen and is immunogenic) versus MUC1 transgenic mice, and what effect such responses have on growth of subcutaneous tumors expressing MUC1. We find that vaccines based on MUC1 synthetic **peptide** and adjuvants such as SBAS2 or GM-CSF induce high titer IgG responses while **peptide** -pulsed DC (free of soluble **peptide**) vaccines do not. The addition of soluble **peptide** to the DC vaccine elicits IgG antibody responses as well. In conventional mice, the DC vaccine results in the induction of both CD4+ and CD8+ IFN-gamma producing MUC1-specific T cells responses and tumor rejection. In MUC1 transgenic mice however, the DC vaccine is capable of inducing only CD8+ responses. Moreover, even though T helper cell tolerance is not overcome, the vaccine does result in tumor rejection. We are currently investigating the need for MUC1-specific CD4+ T cells for long term memory generation. Our preliminary data suggest that activation of CD8+ T cells alone gives long term protection from tumor growth.

ABSTRACT: MUC1 is a tumor antigen expressed by breast, pancreatic, colon, lung and ovarian adenocarcinomas. In **cancer patients** , it is possible to detect **low** titer MUC1-specific IgM antibody and **low frequency CTL** responses. There are no detectable MUC1-specific CD4+ T helper responses which suggests tolerance to...

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8/3,K,AB/14 (Item 1 from file: 34)

11167981 Genuine Article#: 614UZ Number of References: 42
Title: Cytolytic T-cell responses of cancer patients **vaccinated with a MAGE antigen** (ABSTRACT AVAILABLE)
Author(s): Coulie PG (REPRINT) ; Karanikas V; Lurquin C; Colau D; Connerotte T; Hanagiri T; Van Pel A; Lucas S; Godelaine D; Lonchay C; Marchand M; van Baren N; Boon T
Corporate Source: Univ Louvain,Inst Cellular Pathol, Cellular Genet Unit,Ave Hippocrate 74,UCL 7459/B-1200 Brussels//Belgium/ (REPRINT); Univ Louvain,Inst Cellular Pathol, Cellular Genet Unit,B-1200 Brussels//Belgium/; Ludwig Inst Canc Res,Brussels Branch,Brussels//Belgium/
Journal: IMMUNOLOGICAL REVIEWS, 2002, V188 (OCT), P33-42
ISSN: 0105-2896 Publication date: 20021000
Publisher: BLACKWELL MUNKSGAARD, 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK
Language: English Document Type: REVIEW
Abstract: 'Cancer-germline' genes such as the MAGE gene family are expressed in many tumors and in male germline cells but not in normal tissues. They encode shared tumor-specific antigens, which have been used in therapeutic vaccination trials of metastatic melanoma patients. To establish whether there is a correlation between tumoral regressions and T-cell responses against the vaccine antigen, we evaluated the responses of patients vaccinated with a MAGE-3 antigenic **peptide** or a recombinant virus coding for the **peptide** . Blood lymphocytes were stimulated with antigenic **peptide** followed by detection with tetramer, T-cell cloning, and TCR analysis. In 4/9 regressor patients and in 1/14 progressors we found a **low** level, usually monoclonal cytolytic T lymphocyte response against the MAGE-3 **peptide** .

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...Identifiers--GENE MAGE-3; CUTANEOUS MELANOMA; HIGH- **FREQUENCY** ; TUMOR-ANTIGEN; **CTL** CLONES; LYMPHOCYTES; BLOOD; IDENTIFICATION; REGRESSION; MOLECULES

8/3,K,AB/15 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09919491 Genuine Article#: 464EW Number of References: 55
Title: Epstein-Barr virus-specific cytotoxic T lymphocyte responses in the blood and tumor **site of Hodgkin's disease** patients : **Implications for a T-cell-based therapy** (ABSTRACT AVAILABLE)
Author(s): Chapman ALN; Rickinson AB; Thomas WA; Jarrett RF; Crocker J; Lee SP (REPRINT)
Corporate Source: Univ Birmingham,CRC, Inst Canc Studies,Vincent Dr,Edgbaston/Birmingham B15 2TT/W Midlands/England/ (REPRINT); Univ Birmingham,CRC, Inst Canc Studies,Birmingham B15 2TT/W Midlands/England/; Sch Vet,Dept Vet Pathol, Leukaemia Res Fund Virus

Ctr,Glasgow G61 1QH/Lanark/Scotland/; Birmingham Heartlands Hosp,Dept Cellular Pathol,Birmingham B9 5SS/W Midlands/England/
Journal: CANCER RESEARCH, 2001, V61, N16 (AUG 15), P6219-6226
ISSN: 0008-5472 Publication date: 20010815
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202 USA
Language: English Document Type: ARTICLE
Abstract: Approximately 40% of Hodgkin's disease (HD) cases carry EBV in the malignant Hodgkin-Reed Sternberg (H-RS) cells, with expression of viral latent membrane proteins (LMPs) 1 and 2. These viral proteins are targets for CTLs in healthy EBV carriers, and their expression in EBV-associated HD raises the possibility of targeting them for a CTL-based immunotherapy. Here we characterize the CTL response to EBV latent antigens in both the blood and **tumor** -infiltrating lymphocytes of HD **patients** using two approaches: (a) in vitro reactivation of CTLs by stimulation with the autologous EBV-transformed lymphoblastoid cell line; and (b) an enzyme-linked immunospot assay to quantify **frequencies** of **CTLs** specific for known LMP1/2 epitopes. We detected EBV-specific CTLs in blood and biopsy samples from both EBV-negative and EBV-positive HD patients. However, as in healthy EBV carriers, LMP-specific **CTL** precursors occurred only at **low frequency** in the blood of HD patients, and with the exception of one EBV-negative HD case, were undetectable in the tumor. These data give rise to two considerations: (a) they may explain why EBV-positive tumor cells persist in the presence of an existing EBV-specific immune response; and (b) they provide a rationale for selectively boosting/eliciting LMP-specific CTL responses as a therapy for EBV-positive HD.

Title: Epstein-Barr virus-specific cytotoxic T lymphocyte responses in the blood and tumor **site of Hodgkin's dis**ease patients **: Implications for a T-cell-based therapy**
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...Identifiers--STERNBERG CELLS; COMPLEX CLASS-I; IMMUNE RECOGNITION; NUCLEAR ANTIGEN-3; EBV; EXPRESSION; PROTEIN; EPITOPE; IDENTIFICATION; **PEPTIDE**
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$1.98 9 Type(s) in Format 4 (UDF)
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$5.02 0.851 DialUnits File55
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$13.22 Estimated cost File55
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    $74.06   Estimated cost this search
    $74.14   Estimated total session cost    4.253 DialUnits

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